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## Epilepsy &amp; Behavior Case Reports

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## Case Report

## Autoimmune encephalopathy and drug refractory seizures with the presence of two autoantibodies specific for the neuronal cell surface



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## ABSTRACT

**Background:** An increasing number of autoantibodies are being described in epilepsy and other seizure-related disorders. A pathogenic role of autoantibodies in epilepsy has been suggested based on observations of the efficacy of immunotherapy.

**Objective:** This study aimed to report a new case of autoimmune-mediated encephalopathy and seizures caused by autoantibodies to voltage-gated potassium channels (VGKCs) and voltage-gated calcium channels (VGCCs) (P/Q-type) and the response to immunotherapy.

**Design:** This study follows a case report design.

**Setting:** This study was conducted in a tertiary care center.

**Patients:** Our patient was an eighteen-year-old female with new-onset encephalopathy and refractory seizures.

**Intervention:** Our patient was treated for five days with intravenous methylprednisolone (IVMP) and intravenous immunoglobulin (IVIG).

**Results:** After treatment with IVMP and IVIG, our patient showed significant clinical improvement and did not exhibit any seizures during the one-month follow-up period.

**Conclusions:** Here, we report a rare case of an autoimmune encephalopathy and seizures associated with the presence of two surface neuronal autoantibodies. This report highlights the importance of early diagnosis of autoimmune epilepsy, as early immunomodulating treatments improve the outcome.

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## 1. Introduction

Many central nervous system (CNS) disorders characterized by the production of autoantibodies that are directed against cell-surface proteins result in early and prominent seizures that are commonly refractory to conventional antiepileptic drugs (AEDs) but often have a good response to immunotherapies [1].

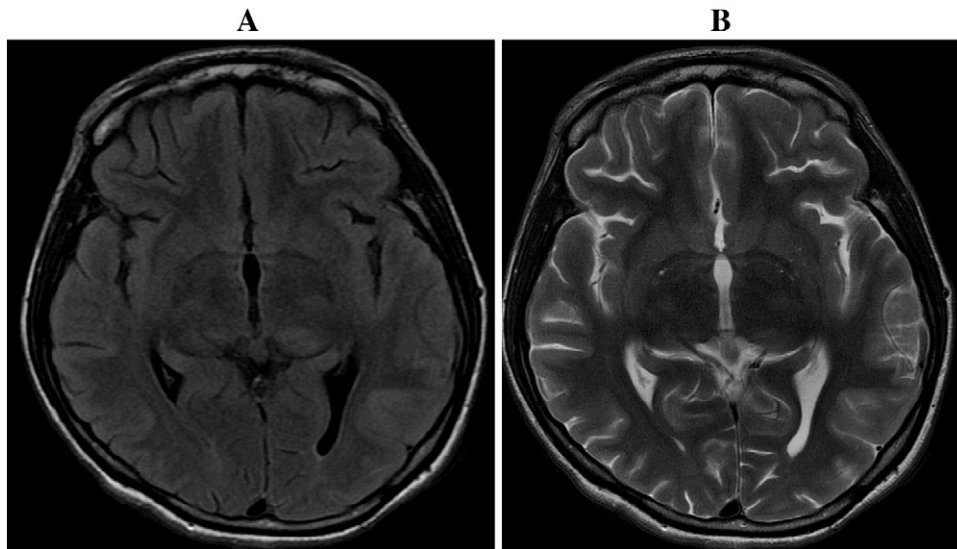
## 2. Case report

An 18-year-old, right-handed female was healthy until 6 weeks prior to observation when she developed new-onset seizures without a clear provocative cause. The seizures started with well-formed visual hallucinations consisting of an aura of seeing strange men entering the room and trying to attack and rape her, followed by vocalization and severe facial grimacing to the right with posturing of both arms with loss of awareness with or without secondary generalization; the seizures were recurrent, arriving in clusters, and not responding to AEDs. Her family had noted a personality change and episodes of confusion

2 weeks prior to the first seizure; it is not clear whether the patient had nonconvulsive status epilepticus or not during those episodes. Her examinations on admission were notable for waxing and waning of confusion and difficulty following complex commands. Four weeks after seizure onset, the patient developed status epilepticus and required intensive care unit (ICU) admission and mechanical ventilation. The cerebrospinal fluid (CSF) revealed 2 white cells/mm [3] with normal CSF protein and glucose levels, and oligoclonal bands were not seen in the CSF or serum. Blood cultures were sterile. Routine blood and inflammatory markers, including serum C reactive protein, were normal except for hyponatremia (sodium, 122 mEq/L). Antibodies against thyroperoxidase (TPO) and thyroglobulin were negative. Antinuclear antibodies (ANA), anti-ds DNA, and anti-SSA and anti-SSB were negative. Brain imaging (CT and MRI) was normal postrecovery from status epilepticus (Figs. A–F). During ICU admission, the patient was connected to a continuous video-electroencephalogram (cEEG) that demonstrated a generalized slow background activity interictally (~4.5 Hz). Five seizures were recorded, all without motor activity, starting in the left occipitoparietal region and spreading to the left hemisphere with secondary generalization. The patient was treated for 5 days with intravenous corticosteroids followed by intravenous immunoglobulin (IVIG). The patient improved significantly after

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**Figs. A–B.** Magnetic resonance imaging (MRI) during status epilepticus shows ictal-related changes. Axial FLAIR and T2-weighted images show hyperintensity involving the cortex of left temporal lobe and left thalamus.

immunotherapy; we were able to wean her off the mechanical ventilation. She was transferred to the neurology ward, and her examinations showed normal higher mental functions without recurrence of seizures over the one-month follow-up period.

Serum autoantibodies were tested by Mayo Medical Laboratories at the Mayo Clinic (Rochester, Minnesota). The test identified the presence of two antibodies against voltage-gated potassium channels (VGKCs) and voltage-gated calcium channels (VGCCs) (P/Q-type).

N-methyl-D-aspartate receptor (NMDA-R) antibodies were not detected.

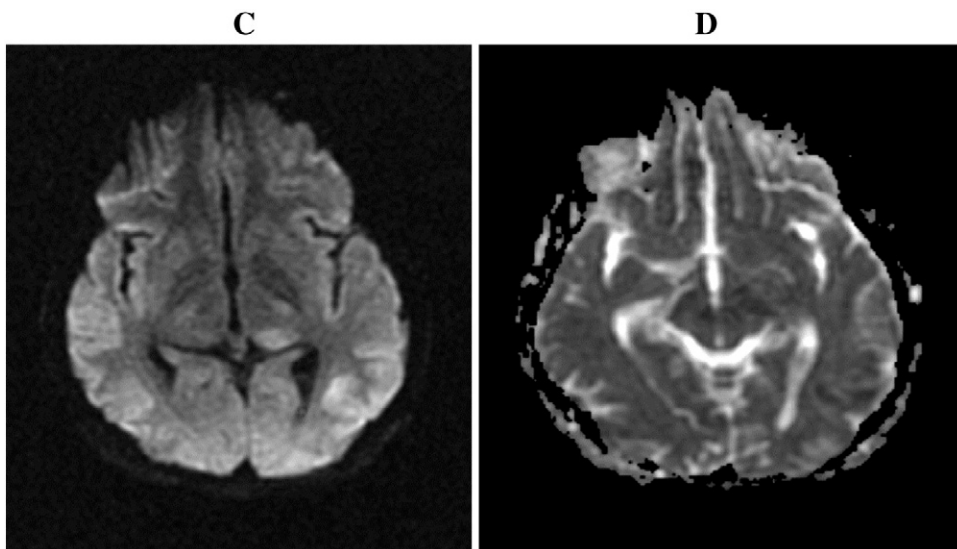
An extensive workup to exclude the neoplastic process was conducted, and imaging using CT, including the chest–abdomen–pelvis, did not reveal any findings. A PET study showed focal intense activity anterior to the esophagus that was worrisome. Further follow-up for this hot spot was stopped because of guardian refusal.

### 3. Comment

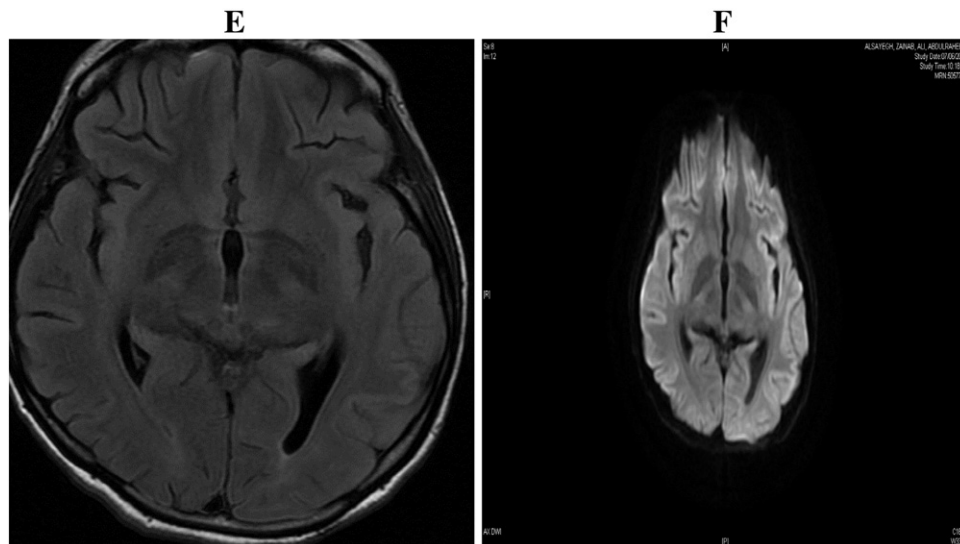
We have described a case of autoimmune encephalopathy and refractory seizures with the presence of two autoantibodies to neuronal cell-surface proteins. The encephalitides associated with antibodies

against cell-surface antigens differ from those related to intracellular antigens in several important respects. First, the cell-surface target antigens are disrupted by the antibodies. Second, the association with malignancy is much less consistent. Third, symptoms can more commonly be reversed with treatment. Finally, the symptoms relate to the disruption of the target antigen [2]. Immune-mediated encephalitides resulting in seizures and status epilepticus are becoming increasingly recognized [3]. Newly identified autoantibody specificities that strongly correlate with clinical seizures include N-methyl-D-aspartate (NMDA) [4],  $\gamma$ -aminobutyric acid B (GABA B receptor) [5], and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [6]. The accumulated data support an autoimmune basis in some patients with AED-resistant seizures [7], including those lacking a typical “limbic encephalitis” phenotype [1,8], and seizures can be the only manifestation without other recognized clinical accompaniments of limbic encephalitis [9].

The diagnosis of autoimmune epilepsy requires a high index of suspicion, and the clues for diagnosis include an unusually high seizure frequency, intraindividual seizure variability or multifocality, AED resistance, and a personal or a family history of autoimmunity [9]. Hyponatremia provides another diagnostic clue favoring an autoimmune



**Figs. C–D.** Axial DWI and ADC map images show restriction diffusion indicated by bright signal on the DWI and dark signal on the ADC map corresponding to the same areas in Figs. A–B.



**Figs. E–F.** MRI image postrecovery from status epilepticus. Axial FLAIR and DWI show resolution of previously seen abnormalities. ADC map and T2-weighted images (not shown) also were normal.

basis for neurologic disease [10] and has been reported in 60% of patients with VGKC autoantibody-associated encephalopathy, reflecting a possible autoimmune hypothalamitis.

Antibodies that bind to the VGKC complex were initially described in patients with peripheral nerve hyperexcitability (neuromyotonia), encephalitis, Morvan syndrome, and various other disorders [11,12]. Very recent experiments have demonstrated that most of the antibodies in the serum of patients with these disorders do not bind directly to VGKCs. Instead, the serum of patients with limbic encephalitis and VGKC-specific antibodies is most often directed against LGI1 leucine-rich glioma-inactivated protein 1, a secreted protein that interacts with several transmembrane synaptic proteins to form a protein complex. Leucine-rich glioma-inactivated-specific antibodies are associated with limbic encephalitis, several types of seizures, and frequent hyponatremia. Mutations of LGI1 are associated with epilepsy [13]. The disorder is rarely paraneoplastic, and the response to treatment is often promising [14,15]. Voltage-gated calcium channel-specific antibodies are strongly associated with Lambert–Eaton myasthenic syndrome, a neuromuscular disorder that typically causes proximal weakness and autonomic symptoms. These symptoms are attributed to the autoimmune disruption of neuromuscular transmission by antibodies specific for P/Q-type VGCCs [16]. Patients with VGCC antibodies may develop a cerebellar syndrome with or without the neuromuscular junction disorder [17]. The presence of VGCC-specific antibodies can also occur in patients with other paraneoplastic neurological disorders or in patients with cancer who do not have a neurological syndrome [18]. In a study of patients with long-standing epilepsy, VGCC-specific antibodies were found in only one patient. Therefore, it is difficult to ascertain whether VGCC-specific antibodies have a direct pathogenic role in epilepsy or simply coexist with epilepsy.

Early immunotherapy will most likely improve the eventual outcomes. In a recent study, all patients exhibiting VGKC-seropositive seizure disorder were responsive to immunotherapy.

Whether the presence of the two surface neuronal autoantibodies had any special effects in this case is difficult to determine, as the number of cases of general autoimmune encephalitis is limited; however, the accumulation of more data with further clinical and paraclinical data may answer this question.

We conclude that an evaluation for the diagnosis of autoimmune epilepsy is critical in patients who present with the appropriate diagnostic clues and that immunotherapy should be started as early as possible.

#### Author contributions

Study concept and design: Al-Ajlan. Acquisition of data: Al-Ajlan, Althobiti, and AL-Attas. Analysis and interpretation of data: Al-Ajlan, Althobiti, AL-Attas, and Baz. Drafting of the manuscript: Al-Ajlan, Althobiti, and AL-Attas. Critical revision of the manuscript for important intellectual content: Baz. Study supervision: Baz.

#### Financial disclosure

None.

#### Conflict of interest

There is no conflict of interest.

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